NOTE

The Oxidation of Optochin

By C. C. Vernon and H. U. Resch

Introduction.—Attempts have been made to reduce the toxicity of optochin[1] by altering the structure of its molecule,[2] since the drug has been shown to have certain desirable properties,[3] and has given promise of being a specific for pneumococci.[4] During such a study in this Laboratory it was necessary to prepare 6-ethoxyquinoline-carboxylic acid-4. In order that there might be no question as to structure, it was proposed to prepare this compound by direct oxidation of optochin. This should be a reliable method, because optochin (ethyl hydrocupreine) closely resembles quinine (methyl cupreine) in structure and chemical properties.[5] Skraup[6] has prepared quininic acid (6-methoxyquinoline-carboxylic acid-4) by the oxidation of quinine, in much the same fashion as described in this article.

Experimental

A solution containing 10 g. (0.029 mole) of optochin and 30 g. (0.328 mole) of sulfuric acid in 200 g. of water was heated to boiling in a flask fitted with a reflux condenser and dropping funnel. A cold saturated solution of chromic oxide in water, containing 20 g. (0.132 mole) in all, was slowly added to the boiling solution, over a period of ninety minutes. Boiling was continued for thirty to sixty minutes, and then sufficient ethyl alcohol was added to reduce the remaining oxidizing agent. The cooled reaction mixture was treated with a solution of 90 g. of potassium hydroxide dissolved in 500 cc. of water, and the gelatinous mass of chromium hydroxide filtered out. The filtrate was exactly neutralized with sulfuric acid, and concentrated to a volume of not more than 300 cc. An equal volume of 95% ethyl alcohol was added and the precipitated potassium sulfate removed by filtration. The alcohol was recovered from the filtrate by distillation and the remaining solution concentrated to approximately 50 cc. over a water-bath. Any precipitate appearing at this point was discarded, and 3 g. (7.1 cc. of a 36% solution) of hydrochloric acid added. After fifteen minutes' heating over a water-bath, yellow needles formed in this solution upon cooling to room temperature. Several crops of these crystals were secured by further concentration of this solution before the residue became so saturated with tarry materials that further treatment was useless.

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[1] Oliver, *Brit. Med. J.*, **1**, 580 (1916); Kolmer and Idzumi, *J. Inf. Dis.*, **26**, 355-371(1920).

[2] Meyer and Gottlieb, "Experimental Pharmacology," Lippincott Company, Philadelphia, 1926, 7th ed., p. 557; Heffter, "Handbuch der experimentellen Pharmakologie," Julius Springer, Berlin, 1920, Vol. II, pt. 1, pp. 96–99.

[3] Woringer, *Arch. de Med. d. enf., Paris*, **27**, 713–725 (1924); Kolmer and Sands, *J. Exp. Med.*, **33**, 693–713 (1921); Morgenroth and Levy, *Berl. Wochenschr.*, **48**, 1561, 1650, 1779, 1983 (1911).

[4] Smith and Fantiss, *J. Pharm. Exptl. Ther.*, **8**, 53 (1916); Weiss, *J. Inf. Dis.*, **22**, 573 (1918).

[5] Heffter, "Handbuch der experimentellen Pharmakologie," Julius Springer, Berlin, 1920, Vol. II, pt. 1, p. 96.

[6] Skraup, *Ber.*, **12**, 1104 (1879).

The product so prepared melted at 231–233°. It was insoluble in ether, chloroform, ethyl acetate and benzene. It crystallized from hot 95% ethyl alcohol in beautiful lemon yellow needles having a final melting point of 288.5°.

Anal. Qualitative: C, H, N, +; S, Cl, −. Calcd. for $C_{12}H_{11}O_3N$: C, 66.35; H, 5.07. Found: C, 66.32; H, 5.00.

The yield of the product melting at 231–233°, as shown in three separate runs, averaged slightly below 20%. The yield of the product melting at 288.5° was approximately 12% of the theoretical. This low yield was believed to be due to the retention of much of the product in the precipitated chromium hydroxide, which was difficult to filter out, and almost impossible to wash.

Summary.—Optochin has been oxidized with chromic oxide in an acid solution. The analysis of the product, and its method of preparation, indicated that it was 6-ethoxyquinoline-carboxylic acid-4.

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COMMUNICATIONS TO THE EDITOR

THE POTENTIAL OF THE Ag(s), AgCl(s), KCl(aq), AgCl(s), Ag(s) CELL, SHOWING THE EFFECT OF FLOWING THE ELECTROLYTE OVER ONE ELECTRODE ONLY

Sir:

Carmody, in a recent note [THIS JOURNAL, **52,** 210 (1932)], states that when the electrloyte is flowing over a Ag(s), AgCl(s) electrode, there is a difference of 0.006 volt positive to a Ag(s), AgCl(s) electrode at equilibrium with the cell solution [p. 191]. This note was written because the value obtained for the Pb, Pb^{++} potential by Randall and Cann [THIS JOURNAL, **52,** 589 (1930)] was 0.1203 v. whereas Carmody [THIS JOURNAL **51,** 2905 (1929)] had obtained the value 0.1263 v. The difference in values was attributed by Carmody to the fact that Randall and Cann had allowed the electrolyte to flow over the Ag(s)–AgCl(s) electrode.

Because of this apparent discrepancy the authors investigated the cell Ag(s), AgCl(s), KCl(aq), AgCl(s), Ag(s), using an H-cell, set up according to Fig. 1, keeping the electrolyte on one side stationary, and allowing it on the other side to be in motion, entering the cell at I and leaving it at II. The Ag(s)–AgCl(s) electrodes were prepared in precisely the same way as had been done previously by Randall and Cann, care being taken to free them from adsorbed gas. The electrodes were white because they were protected from all light. Every operation was performed in containers painted black on the outside. Two cells were made, one containing 0.025 *M* KCl and the other 0.05 *M* KCl. All measurements were made with a Type K potentiometer, using an oil-bath regulated at 25°.